ISSN: 2455 – 5428
International Journal of Current Research and Modern Education
Impact Factor 6.725, Special Issue, January - 2017
International Conference on Smart Approaches in Computer Science Research Arena
On 5th January 2017 Organized By
Department of Computer Science, Sri Sarada College for Women (Autonomous), Salem, Tamilnadu

PHYSICAL AND CHEMICAL PROPERTIES OF THE COCRYSTAL 2-BENZYLAMINO PYRIDINE: OXALIC ACID – A COMPUTATIONAL APPROACH

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Cite This Article: M. Sangeetha & R. Mathammal, "Physical and Chemical Properties of the Cocrystal 2-Benzylamino Pyridine: Oxalic Acid – A Computational Approach", International Journal of Current Research and Modern Education, Special Issue, January, Page Number 15-17, 2017.

Abstract:

In the present work, we report on the enriched physicochemical properties of the cocrystal 2-Benzylamino pyridine: Oxalic acid with the aid of Computational Density Functional Theory. Quantum chemical calculations were performed using the DFT/B3LYP/6-31+G** basis set.The functional groups were obtained from the calculations. The biological application of the compound was determined from the HOMO-LUMO energy gap.The intra-molecular interactions and the charge transfer taking place within the molecule are studied from the NBO analysis.The knowledge about the reactive sites within the molecule and the charge of the atoms are obtained from the Molecular electrostatic potential maps (MEPs).

Key Words: Computational DFT; Cocrystal; HOMO-LUMO Energy Gap & MEP

1. Introduction:

Quantum chemistry is one of the most dynamic fields of contemporary chemistry, providing a solid foundation for all of chemistry and serving as the basis for practical, computational methodologies with applications in virtually all branches of chemistry. Computational chemistry will be restricted to quantum mechanical descriptions of the molecules of interest. It provides the power of high level quantum computations in offering insight towards understanding the nature of organic molecules. The history of drug discovery is characterized by systematic searching for compounds endowed with biological activity by the use of animal models for human diseases. Nowadays, combination of experimental methods for structural determination with theoretical procedures known as computer-aided molecular design (CAMD) which is essential for the development of new drugs aimed at new targets, and thus for medicinal chemistry **[1]**. A variety of computational chemistry method is used in CAMD which comprises mainly two categories of approach- ligand-based and structure-based methods **[2-5].** Within this scenario, theoretical methods based on density functional theory (DFT) are playing an increasingly prominent role in many applications of computational chemistry to drug discovery. Several questions dealing with the electronic structure of the matter are increasingly tackled by means of DFT-based calculations. This approach has intended to study the application of the cocrystal 2-Benzylamino pyridine: Oxalic acid (BAPOA) in pharmaceutical industry.

2. Computational Method:

The entire quantum chemical calculation was carried using Gaussian 09w program package**[6].**The optimization was performed using DFT method and B3LYP functional in combination with 6-31+G** basis set.The normal modes of vibration were calculated from the optimized structure.The normal modes assignmentwas got from the visual animation of the GaussView Program**[7].** The frontier molecular orbital energies, energy gap between various occupied and unoccupied molecular orbitals of title compound are also calculated in the same method with basis set. NBO calculation is also performed on title compound with the same level. The molecular electro static potential (MEP) surface is plotted over the optimized geometry.

3. Result and Discussion:

3.1 Optimized Structure: The cocrystal structure of BAPOA was optimized at DFT/B3LYP/6-31+G** level and shown in **Fig.1.**

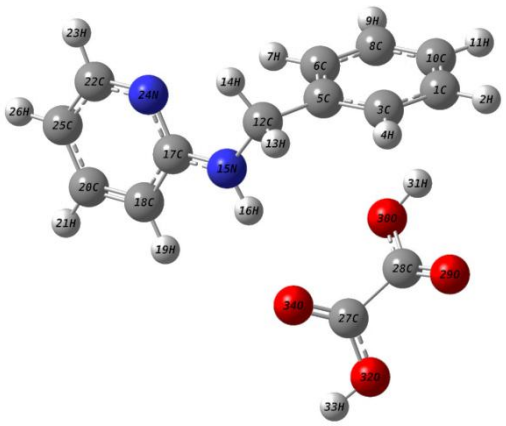

Figure 1: Optimized structure of BAPOA along with atom numbering

3.2 Vibrational Analysis: According to the calculations, the molecule has 34 atoms and 96 normal modes of vibrations.The assignments of vibrational frequencies were made on the basis of the corresponding PEDs by using VEDA program**[8].** The band at 3583cm^{-1} confirmed the hydrogen bonding interaction taking place in the cocrystal.The calculated peaks at 1750 and 1728cm^{-1} are assigned for the C=O stretching modes.The band appeared at 3427cm^{-1} is assigned for N-H stretching.The C-C vibrations are

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calculated at 1579, 1575, 1555 and 1552 cm^{-1}. The bands calculated at 2986 and 2910cm^{-1} are assigned for $–CH_2$ stretching vibrations.

3.3 HOMO-LUMO Analysis: The most important orbitals in the molecule are Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO). The energy gap between the HOMO and LUMO reflect the biological activity of the molecule **[9]**. The HOMO-LUMO energies of BAP and OA were calculated to be -7.86eV, -2.12eV and -6.82eV, -0.16eV respectively. For the cocrystal the energies were determined to be -5.55eV and 2.08eV. On calculating the HOMO-LUMO energy gap for BAP, OA and BAPOA the values were 6.66eV, 5.74eV and 3.47eV respectively. From these data, it is clear that the energy gap for the cocrystal has been significantly reduced promising to be a soft material with high chemical activity. The HOMO-LUMO plots of BAP, OA and BAPOA are displayed in Fig.2. The HOMO-LUMO plot clearly elucidates the eventual charge transfer taking place in the crystal structure. In the HOMO plot the charge is localized over the pyridine ring of BAP molecule and in LUMO plot over the entire OA molecule. This high chemical reactivity influences the biological activity of the compound. Thus the lower value of the energy gap enhances the biological application of the cocrystal.The energy gap between HOMO and LUMO has been used to prove the bioactivity from intramolecular charge transfer [10].

3.4 MEP Map: The MEPs map helps to under the molecular structure and the chemical reactive sites within the molecule. The electrostatic potential and the reactive regions are denoted with different colours ranging in the order red < orange < yellow < green < blue. The colour code for BAPOA molecule was found as -7.808a.u to 7.808a.u. The molecular electrostatic potential map is displayed in Fig.3.

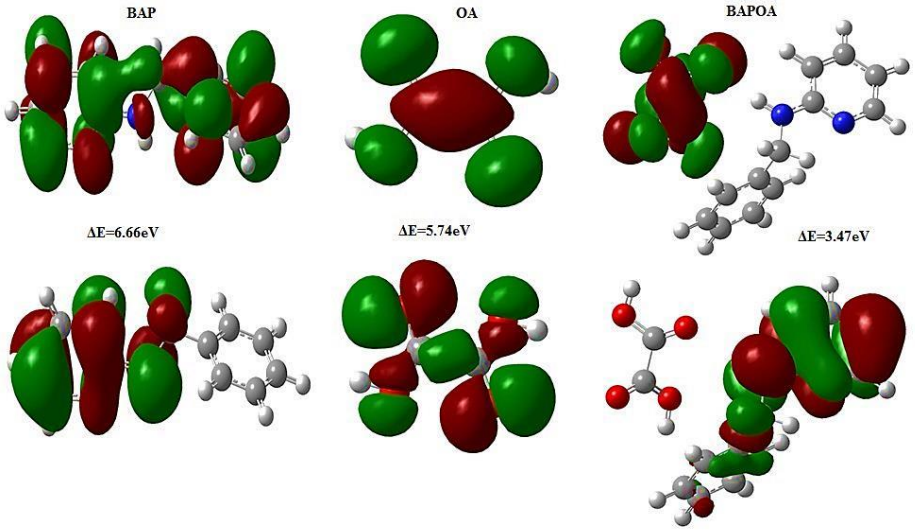
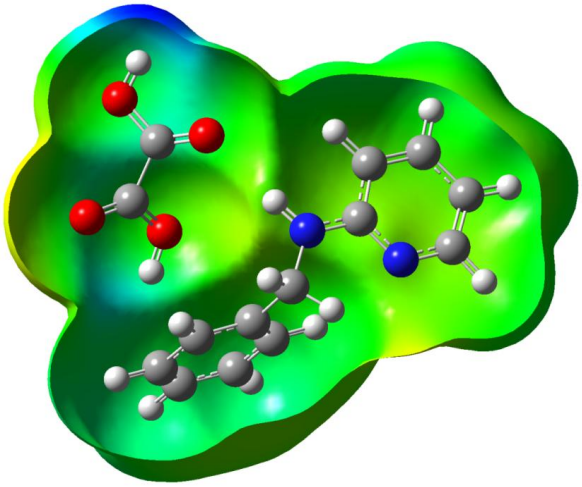


Figure 2: HOMO-LUMO plots of BAP, OA and BAPOA

The blue shade over the hydroxyl group of acid and NH group in BAP molecule denotes the nucleophilic centre and N atom in the pyridine ring with red shade indicates the electrophilic centre. The nucleophilic centre predominantly confirms the intermolecular hydrogen bonding (N-H···O; O-H···O) between BAPOA crystals.



3.5 NBO Studies: NBO analysis has proven a useful tool to investigate intra-molecular or intermolecular interactions [11]. The most stable interaction within the BAP molecule is signified by the n→π* transition occurring between n (N15) to π* (C17-C24) with the maximum stabilization energy 54.48 KJ/mol. The next stabilization is contributed by the N atom in the pyridine ring causing n→ σ* transition with the energy 10.45 KJ/mol. Most of the charge transfer occurred between the π→π* of the C-C bonds in the pyridine and phenyl ring. The strong intermolecular hydrogen bonding between O-H···O determined from XRD well accord

with the NBO results. The utmost stabilization energy within the OA is attributed to n→π* taking place between n (O32) to π* (C27-O34) with the energy 47.72 KJ/mol. This authenticates the intermolecular interaction between the OA molecules. The n→ σ* transition taking part from n (O34) to N15-H16 with the stabilization energy 2.69KJ/mol signifies the inter-molecular hydrogen bonding that stabilizes the crystal structure.

4. Conclusion:

The optimization of the cocrystal was carried out to determine the exact geometrical parameters. The calculated HOMO-LUMO energy gap explored the biological activity of the cocrystal. The various HOMO-LUMO plots explained the type of bonds localized over the molecule.The stabilization energies that held the molecule to form a cocrystal and the charge transfer within the molecule was established from the NBO calculations.The inter-molecular interactions were manifested from the MEP map.

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